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Thrombocytopenia-absent Radius Syndrome with Vitamin B12 Deficiency: Case Report with Literature Review

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Authors' contributions

This work was carried out in collaboration between both authors. Author SF wrote the draft of this case report. Both authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Thrombocytopenia-absent radius syndrome (TAR) is a rare malformation in which thrombocytopenia is associated with lateral radial bone aplasia. The major cause of mortality is hemorrhage which is usually limited to first 14 months of life. Thrombocytopenic episodes decrease as age advances. We present a 22 years old male who was diagnosed as nutritional vitamin B12 deficiency. Despite of giving treatment his platelets did not improve so the patient was reviewed and a revised diagnosis of TAR Syndrome with nutritional vitamin B12 deficiency was made.

Keywords: Rare syndrome; TAR; thrombocytopenia.

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1. INTRODUCTION

Thrombocytopenia- absent radius (TAR) syndrome is a rare congenital disorder first described in 1959 [1] but the current diagnostic criteria for TAR syndrome was given by Hall et al. in 1969 [2]. These include bilateral absence of the radii in the presence of both thumbs and thrombocytopenia [2]. Lower limbs cardiovascular system, gastrointestinal tract ,genitourinary systems could also be involved. Common manifestation is bleeding tendency with high incidence of mortality in neonatal age group [3].

2. CASE REPORT

A 22 year old male presented to hematology clinic with history of weakness, easy fatigability and dyspnea on exertion for 6 months and abnormality in his forearms since birth. No past history of bleeding or hospitalization was noted. Birth history showed normal full term delivery conducted at home. On examination, patient was severely pale without any evidence of ecchymosis or bruising and he was poorly nourished. Regarding his upper limbs deformity in forearms with normal thumbs was noted (Figs. 1a, b). All other systems were normal. Investigations revealed hemoglobin (Hb)-4.1 g/dL, white blood count(WBC)- 2.3× 10^3/ uL, platelets -32 × 10^3/µL, reticulocyte count-1.2%. Peripheral blood smear revealed pancytopenia with hypersegmented neutrophils with no schistocytes. Total bilirubin was 0.8 mg/dL and lactate dehydrogenase: 102 U/l. Serum vitamin B12 level was very low 67.7 pmol/ L (Normal 179 – 660 pmol/L). All other biochemical parameters were normal. Ultrasonography of abdomen showed mild enlargement of spleen and liver. Electrocardiography and echocardiography were normal. Bone marrow examination showed hypercellular marrow with megaloblastic changes and markedly reduced-absent dysmorphic megakaryocytes (Figs. 2 a, b) and a diagnosis of nutritional vitamin B12 deficiency was made. He received packed red blood cells and platelet transfusions and vitamin B12 injections. Patient responded well to treatment as his Hb improved to 11.1 g/dL with WBC -4.2× 10^3 / uL but platelets were still low i.e. 31 × 10^3 / uL.The case was reviewed and X rays performed which showed bilateral absence of the radii with deformed and hypoplastic ulna (Fig. 1c). A revised diagnosis of TAR syndrome with nutritional vitamin B12 deficiency was made and patient was discharged after explaining him the condition. Follow up after 6 weeks also revealed the same platelet count.

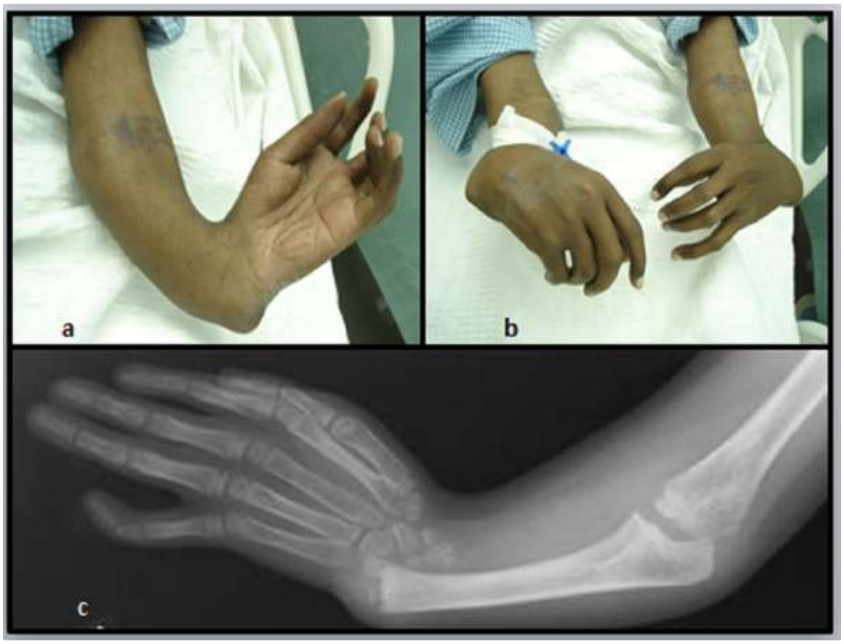

Fig. 1a: Showing deformity of forearm and presence of thumb in TAR Syndrome b: Showing bilateral involvement of upper limbs by deformity c: X ray showing absence of the radii with deformed and hypoplastic ulna

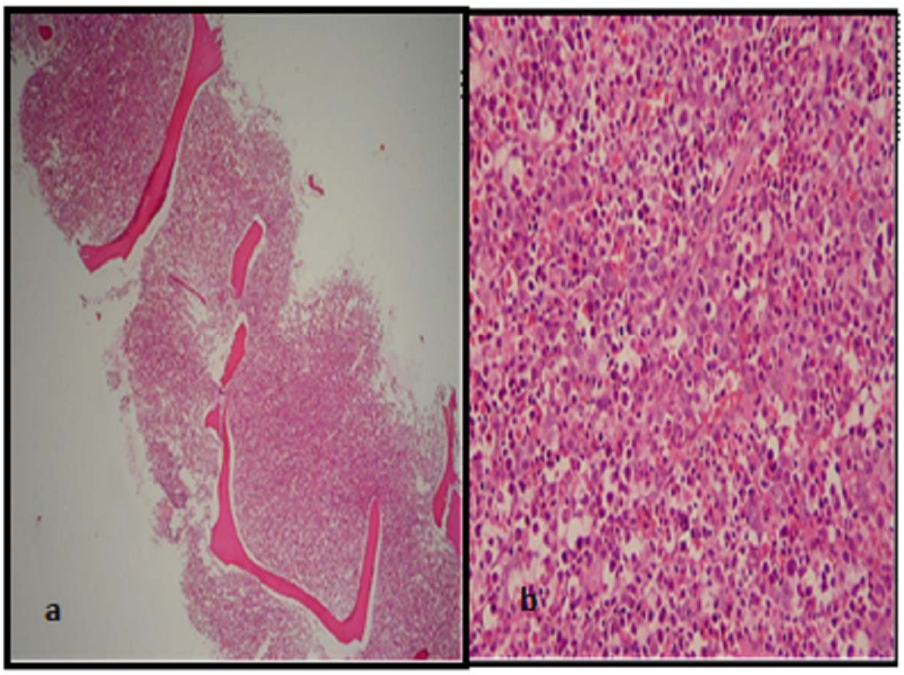

Fig. 2a, b. Bone marrow biopsy showing hypercellular marrow and absence of megakaryocytes (Hematoxylin and eosin, 5X and 40X)

3. DISCUSSION

TAR is a rare autosomal recessive condition and simultaneous development of heart, the radii, and the megakaryocytes at 6-8 weeks of gestation has been proposed as the cause of the combined anomalies [4]. The prevalence of TAR is estimated at 1:200,000–1:100,000 [5]. However, many pregnancies are aborted if TAR is detected therefore the real incidence may be higher. An excess of affected females has also been suggested [3].

Thrombocytopenia may be congenital or may develop within the first few weeks to months of life [5] with neonatal death rate of approximately 40% attributed to hemorrhage. Approximately 50% of affected infants are symptomatic in first week of life and 90% are symptomatic by the age of 4 months [3]. Episodes of thrombocytopenia decrease with increasing age. There are different theories for the exact cause of thrombocytopenia in TAR syndrome. It could be failure in production of humoral or cellular stimulators of megakaryopoesis or due to lack of response to thrombopoietin [6].

Upper limb abnormalities include absence of both radii with presence of thumb, hypoplasia or absence of ulna, hypoplastic humerus with phocomelia. The fingers and thumbs are always present while other skeletal anomalies are frequent [2,3] The upper limb defects can be divided into three categories according to severity. The first group consists of mildly affected subjects presenting with radial aplasia associated with varying degrees of hypoplasia of the ulna and humerus. These patients have a normal shoulder girdle and therefore near normal upper body strength. The second group of moderately affected patients have a greater degree of limb shortening and hypoplasia of the humerus associated with underdevelopment of the shoulder girdle and reduced strength. The final group of most severely affected patients had severe ulnar and humeral shortening with phocomelia. Limb length correlated inversely with independence for daily activities for example, dressing, toiletting and eating [3]. Our patient fulfilled the first category of mild affection. Lower limb deformities range from mild abnormalities such as a small patella leading to subluxation of the knee joint to more severe abnormalities causing bowing of the lower leg, associated with hip, knee, and ankle abnormalities affecting mobility. Reduction defects can also be seen with functional consequence depending on the limb length. Craniofacial features include

brachycephaly, micrognathia, strabismus, ptosis, and a small, upturned nose.

Cardiac anomalies include atrial septal defect, ventricular septal defect, Tetrology of Fallot and patent ductus arteriosus [3,4]. Gastrointestinal problems like cow's milk intolerance [4] presenting as poor weight gain and vomiting, gastroenteritis leading to dehydration can also be seen. Genitourinary abnormalities, growth disorders can also be seen [3]. Renal anomalies such as duplex ureter, renal pelvis dilatation, horseshoe kidney and functional problems (ureterovesical reflux, recurrent pyelonephritis). Mental retardation in TAR syndrome could be due to repeated episodes of intracranial hemorrhage, hypoplasia of cerebellar vermis and corpus callosum [7].

These patients have low platelet count, sometimes eosinophilia and leucocytosis with a shift to left maybe present. Bone marrow in TAR syndrome is normal or hypercellular with decreased megakaryocytes [4].

The other differentials are Fanconi's anemia, Holt-Oram syndrome, Robert syndrome, thalidomide embryopathy and Rapadilino syndrome [5]. In our case anaemia was not secondary to bleeding but was due to vitamin B12 deficiency which was proven by decreased serum B12 levels and later improvement of anemia by vitamin B12 injections. However platelet count remained low which is a part of TAR syndrome.

The genetic basis of TAR syndrome is uncertain.A chromosome 1q21.1 microdeletion was identified in 30 patients affected by TAR syndrome [8]. TAR syndrome has a complex pattern of inheritance associated with a minimal common interstitial microdeletion of 200 Kb on chromosome 1q21. Microdeletion is necessary but not sufficient to cause the phenotype.It has been shown that compound inheritance of a rare null allele and low-frequency non-coding single nucleotide polymorphisms (SNP) in RNA-binding motif protein 8A (RBM8A) are crucial for TAR syndrome [9,10].

Treatment of TAR syndrome includes general supportive care, avoidance of trauma, platelet and blood transfusions. For persistent thrombocytopenia in adults, splenectomy is usually effective. Bone marrow transplantation is an option for resistant cases. Splinting of hand in infancy is helpful. If surgical correction of the arm deformities is indicated, it should be undertaken after the patient is hemodynamically stable. Avoidance of cow's milk is advised as it may precipitate thrombocytopenia [4]. Antifibrinolytic agents and desmopressin acetate (DDAVP) are the drugs used to reduce bleeding and to establish hemostasis. The greatest degree of independence for these patients comes not from surgical, prosthetic or orthotic intervention but from the use of simple adaptive devices and powered mobility aids if required [11].

4. CONCLUSION

TAR is a rare malformation of bilateral absence or hypoplasia of the radius in the presence of both thumbs and a reduction in the number of platelets. The concurrent presence of one of the two non - coding SNPs at one allele and the 1q21.1 deletion at the other is strongly associated with TAR syndrome.

CONSENT

As per international standard or university standard written patient consent has been collected and preserved by the author.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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